Pergamon

Tetrahedron 57 (2001) 2231–2236

TETRAHEDRON

Determination of the absolute stereochemistry of alcohols and amines by NMR of the group directly linked to the chiral derivatizing reagent

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Received 27 October 2000; revised 13 December 2000; accepted 4 January 2001

Abstract—NMR experiments and calculations (PM3) indicate that the asymmetry of the substrate (alcohol or amine) leads to the redistribution of the conformer populations of their methoxyphenylacetic acid (MPA) or methoxytrifluoromethylphenylacetic acid (MTPA) derivatives rather than to the distortion of the conformer geometry as was postulated by Mosher. An absolute configuration of secondary alcohols and primary amines can be determined according to the chemical shifts of the $C_\alpha H$ protons in NMR spectra of their MPA derivatives. The $C_\alpha H$ proton of the diastereomer having a greater relative population of the *sp* form should resonate at a lower field.

1. Introduction

A survey of the recent chemical literature reveals an explosion of an interest in design of chiral derivatizing reagents (CDR) to access an enantiomeric purity and in the determination of the absolute configuration of organic compounds by NMR (^1H, ^{19}F, ^{13}C, ^{31}P, ^{77}Se).[1] The differentiation of the NMR signals of the diastereomers[2] or diastereotopic complexes[3] obtained by the reaction of the CDR (with the known absolute configuration) with the substrate molecule is used to determine the absolute configuration of the latter. Theories that correlate an absolute configuration and NMR chemical shifts of the substrate fragment have been developed.[4] These models exploit the selective shielding effect of the aryl group of the CDR on the nuclei of the substrate part of the obtained diastereomer. The relative chemical shifts of the substrate protons would depend on the relative spatial arrangement of the substrate fragment and the aryl group of the CDR part of the diastereomer as well as on the absolute configuration of both chiral centers.

At the same time, attempts to find an empirical correlation between NMR parameters of the CDR moiety of the diastereomer and the configuration of the substrate are known.[4a,5] For example, in the case of alcohols, the idea of using NMR of the acid moiety of a derived ester is very attractive due to the fact that usually the NMR signals do not overlap with other resonances. Only Mosher, however, gave a reasonable interpretation of the ^{19}F NMR chemical shifts of methoxytrifluoromethylphenylacetic acid (MTPA) derivatives of secondary alcohols and primary amines and proposed the model to determine an absolute configuration by ^{19}F NMR of the CF_3 group in the case of MTPA.[4a,5]

According to Mosher, the MTPA-esters in solution exist in a single form, where the C_α–CF_3 bond is, approximately, *syn-periplanar* to the C=O bond. Due to the difference of steric interactions between bulky substituents of alcohol and acid moieties in (*R*)- and (*S*)-esters that leads to distortion of the 'classical' conformation (Fig. 1) there is some difference of the CF_3–C_α–C=O angles. Therefore, the observed difference between the ^{19}F NMR chemical shifts of the (*R*)- and (*S*)-MTPA esters was explained as a result of different anisotropic deshielding effects of the C=O bond on the CF_3 group in these diastereomers.

This model has been used to explain the difference of ^{19}F NMR chemical shifts of the (*S*)- and (*R*)-MTPA-esters. It was found that in the series of similar derivatives when the interactions of MTPA and alcohol moieties do not vary, the differentiation of their ^{19}F NMR chemical shifts should also be very similar. Thus, provided the stereochemistry of one compound is known, the stereochemistry in a whole series

Keywords: absolute stereochemistry; NMR; chiral derivatizing reagents; methoxyphenylacetic acid; methoxytrifluoromethylphenylacetic acid.
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0040–4020/01/$ - see front matter
PII: S0040-4020(01)00056-4